

REMARKS/ARGUMENTS

Claim Status

Claims 1-32 are pending in the application. Claims 25-31 have been renumbered, because of an inadvertent error in claim numbering at the time of filing this application. As filed, there were two (2) claims numbered 25. The instant amendment corrects this error by numbering the second claim 25 as claim 26, and correcting the numbering of the subsequent claims. Since this amendment results in an additional dependant claim fee, an attached fee transmittal is believed to correct this error.

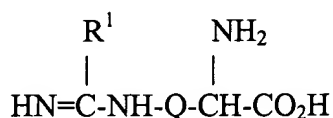
No other amendments have been made to the claims.

Rejection Under 35 U.S.C. § 103(a)

Renumbered claims 1-32 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Beams et al., WO 93/13055. For the following reasons, this rejection is traversed.

A. Viewed as a Whole, WO 93/13055 does not Teach or Suggest the Instant Invention

Beams et al., WO 93/13055, does not teach or suggest the compounds as claimed in the instant application. Beams et al. gives no direction to make the 4,5 double bond in a heptene carbon chain, as is claimed in the instant application, but rather proposes a large number of possible substitutions in a variable core central to the molecules. It was pointed out in Paper Number 13 that in Beams et al., an embodiment of the formula at page 6, lines 30-36 was as follows:



wherein

Q is $-(CH_2)_n$ where n is 3 to 5,

Q is $-(CH_2)_vCH=CH(CH_2)_w$ and

Q is $-(CH_2)_vC\equiv C(CH_2)_w$

wherein in each case, v is 0 to 3, w is 0 to 3, with the proviso that the sum total of v and w is 2 to 4

Thus there are three choices for alkylenes, four choices for v (0, 1, 2, or 3), four choices for w (0, 1, 2 or 3), with the proviso that both v and w cannot both simultaneously be 3, and if either v or w is 2, then the other cannot be 3, and if v is 0, the w cannot be 0 or 1, and if w is 0, then v cannot be 0 or 1 (in other words, six possible combinations of v and w are not allowed.). Therefore, there are ten remaining choices for alkenylenes, and ten remaining choices for alkynylenes.

It was stated in Paper Number 13 that the instantly claimed compounds correspond to v=2 and w=1. This is true, however, only when R¹ and R² are H, corresponding to claims 3, 11 and 19. In other claims, such as claims 7, 15, 23, and some compounds of claim 29 (renumbered), v= 2 and CH₃ and w=1 and CH₃. One skilled in the art would be taught away from these compounds by the teaching of Beams et al.

While Beams et al. shows a preferred group of formula I as having R¹ is methyl, the other preferred groups are described as follows:

Q represents $-(CH_2)_n-$ where n is 3 or 4;

$-CH_2CH=CHCH_2-$;

$-(CH_2)_2SCH_2-$; or

$-CH_2ACH_2-$ where A is cyclopropyl;

and pharmaceutically acceptable salts, esters and amides thereof.

Specific preferred compounds of formula (I) are:

(S)-N³-(1-iminoethyl)ornithine;

(S)-N⁶-(1-iminoethyl)lysine;

(±)-E-2-amino-6-(1-iminoethylamino)-hex-4-enoic acid;

and

(S)-S-2-(1-iminoethylamino)ethylcysteine

and pharmaceutically acceptable salts, esters and amides thereof.

Finally, while it is acknowledged that Beams exemplifies an olefin group in examples 3 and 8, both of these examples are hex-4-enoic acids (as described as "preferred" on page 7 of Beams. It was asserted in Paper number 13 that the instant invention is an adjacent homolog of the exemplified compounds of Beams et al. An insertion of a methylene into the exemplified compounds of Beams et al. could result in a number of compounds other than the instantly claimed compounds. Likewise, a deletion of a methylene from the exemplified compounds in Beams et al. would result in a number of compounds other than the instantly claimed compounds. When R^1 and R^2 are other than H, there is more than a methylene insertion in the chain, making these compounds even less structurally similar to anything taught or suggested by Beams et al.

Thus, there is no teaching in Beams et al. that would direct one of ordinary skill in the art to make the compounds of the instant invention.

B. The State of the Art, at the Time of Filing of the Instant Application Teaches Away from the Claimed Compounds.

The instant specification provides the following background at page 4, lines 7-11:

Various attempts have been made to improve the potency and selectivity of NOS inhibitors by adding one or more rigidifying elements to the inhibitor's structure. Publications by Y. Lee et al (Bioorg. Med. Chem. 7, 1097 (1999)) and R. J. Young et al (Bioorg. Med. Chem. Lett. 10, 597 (2000)) teach that imposing conformational rigidity with one or more carbon-carbon double bonds is not a favorable approach to impart selectivity for NOS inhibitors.

Specifically, at page 1101, the Lee reference states:

Conclusion

On the basis of the results reported here and those by Shearer et al.¹⁷ conformational restriction appears to prevent the molecules from assuming the appropriate discriminatory binding orientations needed for high selectivity of the isozymes of NOS.

At page 600, first paragraph, the Young reference states: "It has also been suggested that imposing conformational rigidity is not a favourable approach to impart selectivity."

For the Examiner's convenience, both of these references are attached to this Amendment.

Thus, at the time of filing of the instant application, at least two literature references were available that were skeptical of the use of rigidifying elements, such as the carbon-carbon double bonds taught in the instant application.

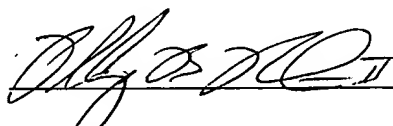
Significantly, two of the authors of the second literature reference (Bioorg. Med. Chem. Lett. 10, 597 (2000)), Harold F. Hodson and Richard M. Beams, are among the three inventors of WO 93-13055. Therefore, this later reference teaches away from the olefinic compounds of the present invention.

Conclusion

In view of the above, it is submitted that Claims 1-32 are in condition for allowance. Reconsideration of the rejections and objections is requested, and allowance of Claims 1-32 at an early date is solicited.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, he is cordially invited to contact Applicant's representative at the below listed number.

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